Cost and Healthcare Resource Utilization (HRU) Among Patients Living with Angelman Syndrome (AS): A Systematic Review

Authors: Vyshnavi Telukuntla, Rishabh Verma, Nidhun Kandoth, Sukannya Mahapatra, Amit Ahuja and Inderpreet Khurana

Affiliations: Lumanity, Gurugram, India

INTRODUCTION

- Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by loss of *UBE3A* expression in neurons.[1] Patients exhibit intellectual disability, balance disorders, behavioural issues, seizures, sleep disturbances, and speech impairment[2]
- The most common genetic cause is a deletion on chromosome 15q11-q13 encompassing the *UBE3A* gene. Other causes include pathogenic variants in *UBE3A*, imprinting defects, and paternal uniparental disomy for chromosome 15, collectively known as non-deletion AS
- Most patients with AS have an approximately 4 Mb maternal deletion of 15q11-q13 (Class I). Others have paternal uniparental disomy of chromosome 15 (Class II), imprinting defects (Class III), or UBE3A mutations (Class IV)[3]
- In healthy individuals, certain genes are expressed only when they are inherited from a specific parent (i.e. the genes are imprinted). One of these imprinted genes is *UBE3A*, which is expressed only when it is inherited from the mother[4]

OBJECTIVES

To examine costs and healthcare resource utilization (HCRU) for treatment of individuals with AS

METHODS

- Embase® and MEDLINE® databases were systematically searched via Embase.com, in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines, by pairing relevant keywords to identify English-language studies reporting costs and HCRU in patients with AS
- Publications were limited to those reporting information on cost and HCRU among adult patients with AS, as per pre-defined inclusion criteria presented in **Table 1**
- Two independent reviewers performed initial screening of title and abstract from the database search. Each potentially relevant record was further screened in full by two independent reviewers. Any uncertainty regarding the inclusion of a record was reconciled by a third reviewer

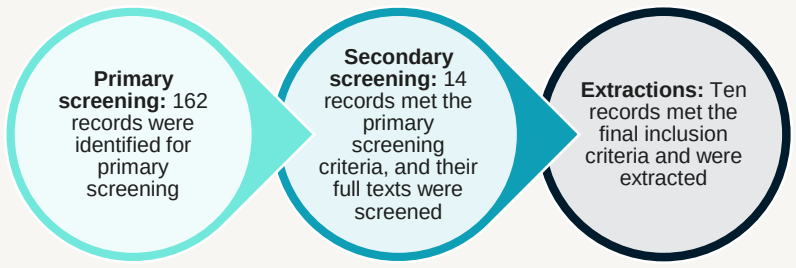
Table 1. Inclusion criteria

Population	Adults and children with Angelman syndrome
Intervention and comparator	No restriction
Outcomes	Cost and resource use
Study design	Cost studies, Resource use studies, Cost/economic studies, Economic evaluations reporting cost or resource use, Budget impact analysis, Cost–benefit, cost consequence and cost-minimization analysis, Cost–utility analysis
Country	No restrictions
Language	English

RESULTS

- A total of 162 records were screened using the predefined population, intervention, comparison, outcomes and study-based criteria; 10 studies were identified and included that evaluated the economic burden of AS **(Figure 1)**

Figure 1. Study flow diagram



- Out of 10 included studies, seven[5-11] were conducted in the US, two[12,13] were conducted in Australia, and one[14] study was conducted in Spain. Of the 10 included studies, only one study reported cost data; the others provided data on HCRU
- The evidence was primarily derived from observational/real-world studies, including five longitudinal observational (50%), two retrospective (20%) and two cross-sectional studies (20%). One study (10%) did not report the study design. The sample size ranged from seven[10] to 492[13] patients

Costs associated with AS in Australia

- Baker et al. 2023[12] compared the total societal cost of treatment for four rare disorders, including fragile X and chromosome 15 imprinting disorders such as AS, fragile X syndrome, Prader–Willi syndrome and chromosome 15q duplication syndrome. Of the investigated conditions, AS incurred the highest mean cost per person (AUD 96,988; 95% confidence interval [CI]: 59,025, 134,951)
- The total cost of AS treatment was significantly higher in patients who had a higher intellectual functioning. This was contrary to the trend observed in patients with other syndromes (Prader–Willi, chromosome 15q duplication, and fragile X syndromes), where higher intellectual functioning was associated with a reduced cost of treatment
- The cost drivers for AS were group home/residential care living, lost employment/employment taxation, and out-of-home care. The direct and indirect costs are reported in **Table 2**

HCRU – US

- The mean number of hospitalizations was 2.3 (95% CI: 2.1, 2.5), with an average length of stay (LOS) of 4.5 days[8]
- 57% of participants with AS in this study underwent at least one surgery. The most common surgeries were insertion of ear tubes (34%), correction of strabismus (30%), tonsillectomy/adenoidectomy (25%), and gastrostomy tube insertion/fundoplication (8%)[8]

HCRU – Spain

- 85.7% (n = 42) of patients were hospitalized at least once from 2006 to 2014. The most frequent causes of hospitalization were oral–dental care (28.9%), seizures (19.6%), orthopaedic problems (14.4%), acute respiratory disorders (12.4%), and others (24.7%)[14] **(Figure 2)**
- Hospitalization for acute respiratory disorder was higher in adults (34.8% in people aged 18 years or older versus 5.4% in people below 18 years of age; p-value < 0.05). The median LOS was 8.5 days[14]

Table 2. Mean costs associated with Angelman syndrome in Australia

Category	Cost in AUD (Range)
Direct costs	
Out-of-home care	15,738 (1,921–29,553)
Cost of purchasing and renting equipment	430 (276–584)
Inpatient and emergency department hospital admissions	4,794 (-360–9,947)
Outpatient visits	5,181 (2,901–7,462)
Cost of medications	587 (364–810)
Group home/residential care living	28,449 (-2,775–59,674)
Transportation	1,502 (687–2,317)
Indirect cost	
Lost employment/employment taxation	19,367 (7,785–30,949)
Special education	5,288 (868–9,707)
Government benefits	9,149 (3,668–14,631)
Informal care (excluding primary caregivers)	8,320 (1,524–15,116)
Societal cost	
Total cost to government	72,870 (39,554–106,187)
Total cost to individual/family	24,118 (14,346–33,889)

Deletion and non-deletion genotypes – US

- The mean number of hospitalizations was comparable for deletion and non-deletion patients (2.3, 95% CI: 2.0, 2.5 versus 2.4, 95% CI: 2.0, 2.9; p = 0.7099). There were also no statistically significant difference between deletion and non-deletion patients in terms of LOS (4.1 days versus 5.5 days; p = 0.1300)[8]
- Deletion and non-deletion cohorts reported similar rates, mean number, and reasons for all surgeries expect for strabismus, which was significantly more common in the deletion cohort compared with the non-deletion cohort (36% versus 18%; p = 0.0814)[8]

HCRU stratified by age and sex

- In the US, the mean number of hospitalizations decreased by 27%, from 1.5 at 1 year to 1.1 at 12 years of age. Among those hospitalized, the mean LOS was 6.5 (standard deviation [SD]: 8.9) days at 1 year, 3.6 (SD: 5.8) days at 6 years and 1.5 (SD: 0.71) days at 12 years of age[8] **(Figure 3)**
- In Spain, the percentage of hospitalizations was higher in women than in men for oral–dental care (39.7% versus 12.8%, p < 0.05) and seizures (20.7% versus 17.9%), and lower in women than men for orthopaedic problems (6.9% versus 25.6%, p < 0.05) and acute respiratory disorder (10.3% versus 15.4%)[14] **(Figure 4)**

Figure 2. Causes of hospitalizations in Angelman syndrome

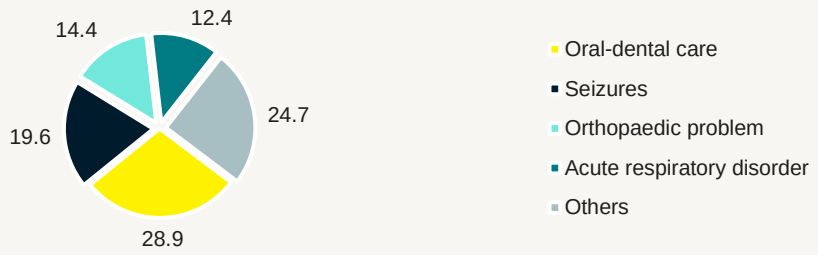


Figure 3. Mean healthcare utilization by age Angelman syndrome

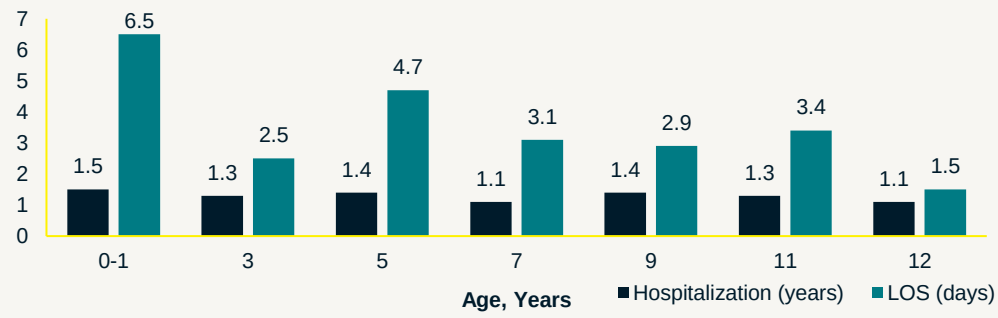
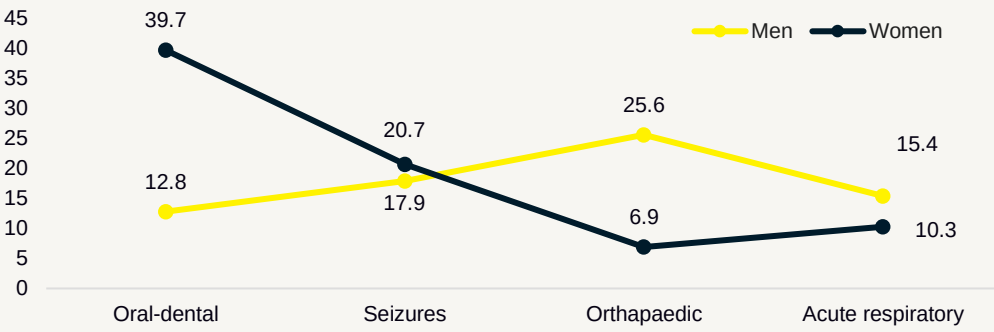


Figure 4. Causes of hospitalizations in Angelman syndrome



CONCLUSIONS

- The significant costs associated with AS are linked to the severity of intellectual functioning. Reductions in total yearly costs are linked to intellectual functioning, suggesting that earlier diagnosis and targeted interventions could reduce the economic burden of AS on health systems
- The higher rates of HCRU in individuals with AS highlight a noticeable healthcare burden. Younger children (especially those in their first year) tend to experience more surgeries, more hospitalizations and longer hospital stays than older children with AS. Moreover, differences in the causes of hospitalization were observed by age and sex

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An electronic version of the poster can be viewed by scanning the QR code.

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